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HOVEY, WILLIAMS, TIMMONS & COLLINS
SUITE 400
2405 GRAND BLVD.
KANSAS CITY, MO 64108

EXAMINER	
SRIVASTAVA, KAILASH C	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 01/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/037,772	STOUT ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *0/18/2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,12,14-20 and 22-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,12,14-20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response and amendment filed 18 October 2004 to Office Action mailed 16 April 2004 is acknowledged and entered. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office action.

2. For the record, Applicants' response cited *supra* is inconsistent and not completely clear. At many places in their arguments or discussion, applicants have not properly referenced the Office Action to which they are responding, or a particular rejection that they are arguing about (e.g., Under Remarks, at Page 7, line 2, "in the most recent Office Action"; At Page 7, Paragraph 3, Line 1,"rejected at least some of the claims"). Please ensure that in all future correspondence with this Office a proper reference is made to the Office Action/ Claim(s) that is being discussed in a response or against which the arguments are made. Examiner is proceeding with the Office Action *infra* only to avoid delays and expedite the prosecution.

CLAIMS STATUS

3. Claims 2, 11, 13, 21 and 25-51 are cancelled.

4. Contrary to applicants' indication in Claim listing, Claims 1 and 12 have been amended.

5. Claims 1, 3-10, 12, 14-20 and 22-24 are pending and are examined on merits.

Election/ Restriction

6. Contrary to applicants' assertion (See page 7, Paragraph 1, Lines 1-2 of response cited *supra*), in the Office Action mailed 16 April 2004, Examiner reiterated the Restriction/Election requirement according to the Office Action mailed 15 September 2003 in view of applicants' amendment and response filed 14 January 2004, wherein a new Claim, Claim 51 was added. Applicants to note that Examiner did not make a new restriction requirement in the Office Action mailed 16 April 2004.

Claims Objection

7. In response filed 20 October 2004, following Claims do not comply with 37 CFR §1.121. Effective July 30, 2003 all claims in an amendment should be listed with a proper identifier and markings *(See, 68 Fed. Reg. 38611 (June 30,2003), 1272 Off. Gaz. Pat. Office 197 (July 29, 2003)(final rule).*

- Claims 1 and 12 are not indicated with a proper status identifier, because Claims 1 and 12 have been amended.

- Claim 12 is improperly presented because deletions should be crossed out, not bracketed (See Line 7, word [and].

8. Claim 3 objected to because of the following informalities:

- Claim 3 objected to under 37 CFR §1.75(c), as being of improper dependent form because Claim 3 depends from a cancelled claim (i.e., Claim 2). Applicant is required to cancel, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

First Paragraph Rejections

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> ***The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.***

10. Claims 1, 3-10, 12, 14-20 and 22-24 rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to a method to determine/ screen a drug, i.e., a chemical compound, wherein said compound modifies the activity of an enzyme on a given substrate, wherein the substrate, enzyme and said drug are present in a given fluid. In said method, sample taken from a patient who may or may not be on said drug is compared with a standard, wherein said standard is a sample taken from a patient who is known to be taking a certain dose of the test drug.

From the record of the present written disclosure, the specification, while enabling for a method to determine an ACE inhibitor drug in a serum or a urine sample (See Examples 1 and 2 in Specification, Page 7, Line 6 to Page 11, Line 10) does not reasonably teach a method to determine the presence in any fluid of each and every active drug/chemical compound that modifies the activity level of an enzyme on a selected substrate, wherein sample taken from a patient who may or may not be on said drug is compared with a standard, wherein said standard is a sample taken from a patient who is known to be taking a certain dose of the test drug. Also, there is no example showing correlation of data from examples 1 and 2. Thus, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to extrapolate the claimed invention method to

determine presence of any or all drugs/chemical compounds modulating activity of any or all enzyme, in any or all biological fluids (e.g., cerebrospinal fluid) obtained from one or more patients, whether said patients are, or are not on the drug being tested.

A person of skill would not be able to practice the invention to determine a drug/compound that modulates the activity of an enzyme as claimed because in absence of a teaching about the results obtained from the method of claimed invention without undue experimentation. Undue experimentation will be required to obtain a pattern of claimed parameter(s) (i.e., modulation of the activity of any or all enzymes in any or all fluids in presence of any or all drugs/compound) due to the quantity of experimentation necessary; limited amount of guidance as to how to extrapolate the information from Examples 1 and 2, and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

11. Amended Claim 1 and Claims 3-9 rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with those claims. The claims are directed to a method to determine/ screen a drug, i.e., a chemical compound, wherein said compound modifies the activity of an enzyme on a given substrate, wherein the substrate, enzyme and said drug are present in a given fluid.

From the record of the present written disclosure, the specification, while enabling for a method to determine an ACE inhibitor drug in a serum or a urine sample (See Examples 1 and 2 in Specification, Page7, Line 6 to Page 11, Line 10) does not reasonably teach a method to determine the presence in any fluid of each and every active drug/chemical compound that modifies the activity level of an enzyme on a selected substrate, wherein all the reactants, i.e., said enzyme, substrate or drug are present in a fluid. Furthermore, the examples in the specification demonstrate a method to identify the presence of only ACE-inhibiting class of drugs in a urine sample (See for e.g., specification, Tables 1, 2 and Page 11, Lines 1- 10) without showing any results on the effects of any other class of drugs/chemical compounds on modifying any other enzyme or any other fluid aside from urine and serum. Furthermore, there is no example showing correlation of data from examples 1 and 2. Thus, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to extrapolate the claimed invention method to determine presence of any or all drugs/chemical compounds modulating activity of any or all enzyme, wherein all the reactants are present in any or all biological fluids (e.g., cerebrospinal fluid) obtained from one or more patients, whether said patients are, or are not on the drug being tested.

A person of skill would not be able to practice the invention to determine a drug/compound that modulates the activity of an enzyme as claimed because in absence of a teaching about the results obtained from the method of claimed invention with other enzymes or drugs or compounds contained in fluids other than serum or urine, it will be difficult to correlate the results on a specific Class of ACE-inhibitors with any or all enzymes, let alone proteases or angiotensin converting enzyme (i.e., ACE). Undue experimentation will be required to obtain a pattern of claimed parameter(s) (i.e., modulation of the activity of any or all enzymes in any or all fluids in presence of any or all drugs/compound) due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Second Paragraph Rejections

12. Claims 1, 3-10, 12, 14-20 and 22-24 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claims 1 and 12 as currently presented are very confusing, difficult to understand and thus indefinite. Applicants are requested to clearly, concisely and succinctly rewrite the claims in a step-by step fashion indicating clearly how the activities from different samples are measured/compared and what is the real measure of enzyme activity. It seems that mere comparison of said enzyme activity in test sample with a sample taken from another patient will not be a clear indication/ quantification of enzyme activity. As presently written, it is difficult to understand, how on would be able to determine the presence of an active drug, depending on the standard activity from another patient sample if the enzyme activity from the test sample is inhibited or enhanced, Applicants are cautioned not to add any new matter when clearly, concisely and succinctly rewriting said claims.

- Recitation "active drug" in Claim 1 and "active ACE-inhibiting drugs" in Claim 12render those claims unclear, vague and indefinite because the term "active" is a subjective term and therefore, does not establish any metes and bounds. Applicants are requested to define the metes and bounds for the term "active".

All other claims depend directly or indirectly from the rejected claims (e.g., Claim 1 or 12) and are, therefore, also rejected under 35 U.S.C. §112, second paragraph for the reasons set forth above.

Claim Rejections – 35 U.S.C. § 102

13. In view of applicants' amendments and arguments filed 18 October 2004 to Office Action mailed 16 April 2004, Examiner hereby withdraws the rejections under 35 USC § 102 to claims 1-9 as anticipated by Fobare et al. (U.S. Patent 4,792,614); Claims 1-10, 12-18 and 20-23 as anticipated by Yoshikawa et al. (U.S. Patent 5,369,015), and to claims 1-10, 12-18 and 20-22 as anticipated by Brunner et al. (U.S. Patent 5,407,803).

14. The following new rejection is made including new references, Weinshilboum et al. (American Journal of Human Genetics, 1980,Volume 32, Pages 651-662) and Alegret et al. (European Journal of Pharmacology, 1998, Volume 347, Pages 283-291) because the amended Claims 1 and 12 filed 20 October 2004 add new limitation of "comparing the activity of enzyme in a sample taken from a patient that may or may not have the target drug, against the sample taken from another patient known to have taken the target drug, wherein latter sample is taken as the standard. Both, Weinshilboum et al. and Alegret et al. teach said limitations in a method to determine the enzyme activity in samples obtained from two different patients.

15. Claims 1-6 rejected under 35 U.S.C. §102(b) as anticipated by Weinshilboum et al. (American Journal of Human Genetics, 1980, Volume 32, Pages 651-662).

Claims recite a method to compare activity of a given enzyme on a given substrate in a sample obtained from a patient that may or may not be on a target drug, against the sample taken from another patient known to have taken the target drug, wherein latter sample is taken as the standard.

Weinshilboum et al. teach comparing the activity of erythrocyte (i.e., RBC) thiopurine methyltransferase (i.e., TPMT), an enzyme catalyzing thiopurine S methylation, in blood samples taken from 298 different patients. mercaptopurines, i.e., thiopurines (e.g., mercaptopurine) are the drugs used in the treatment of patients with neoplastic and autoimmune diseases. Weinshilboum et al. further teach that on the basis of activity of said enzyme in the population tested, three groups were distinguished (i) undetectable enzyme activity; (ii) intermediate enzyme activity and (iii) high enzyme activity and said data is useful in determining the sensitivity of thiophines to population receiving said treatment (Abstract, Lines 1-16; Page 552, Lines 1-20 and Page, Page 653, Lines 30-37). Note that in said method, since the enzyme activity is being measured on the conversion of 6-mercaptopurine (substrate) to radioactively labeled 6-methyl-mercaptopurine [^{14}C] S-adenosyl-L-methonine (SAM), inherently the substrate amount is known. Thus, the prior art teaches a method to evaluate the enzyme activity to determine a drug employing same steps as claimed in the instant invention.

Therefore, the prior art method inherently must function as claimed (See e.g., In re Best, 195 USPQ 430, 433-CCPA 1977).

Therefore, the reference deems to anticipate claims 1-6.

16. Claims 1-7, 10, 12, 14-18 and 20 rejected under 35 U.S.C. §102(b) as anticipated by Alegret et al. (European Journal of Pharmacology, 1998, Volume 347, Pages 283-291).

Claims recite a method to compare activity of a given enzyme on a given substrate in a sample obtained from a patient that may or may not be on a target drug, against the sample taken from another patient known to have taken the target drug, wherein latter sample is taken as the standard. In said method, the drug is an ACE inhibitor and the activity of the enzyme is determined in different samples at certain time intervals.

Alegret et al. teach a method to assay the activity of 3-hydroxy-3-methyl-glutaryl CoA reductase (i.e., HMG CoA reductase) in samples from different groups of rabbits treated with three different ACE-inhibitors and a control. The activity was monitored over a period of 4 weeks in rabbits treated with bezafibrate, atorvastatin and simvastatin. The control was placebo. Fluidized liver microsomal samples taken from each group were monitored for the activity of HMG CoA reductase concomitant with the levels of plasma cholesterol and triglyceride levels (Abstract, Lines 1-13; Page 284, Column 1, Line 39 to Column 2, Line 5 and Page 284, Column 2, Lines 36-52) Data suggests an inhibition in HMG CoA reductase activity concomitant with lowering of different lipids (i.e., cholesterol; See Figure 1; Page 287, Column 2, Lines 39-41 and Page290, Column 1, Lines 16-20). Note that in said method the activity of an enzyme is monitored in samples taken and measured at different time intervals during the treatment regimen and more than one fluid sample was analyzed with same substrate at each time point of determination. Finally, the data from different determinations is correlated to conclude that statins (i.e., atorvastatin and simvastatin) at a concentration (i.e., dosage) of 3 mg $kg^{-1}day^{-1}$ were effective in inhibiting the HMG CoA reductase activity which corroborated with lowering of cholesterol in concomitantly taken blood/plasma samples from same subjects. Thus, the prior art teaches a method to evaluate the enzyme activity to determine a drug employing same steps as claimed in the instant invention. Therefore, the prior art method inherently must function as claimed (See e.g., In re Best, 195 USPQ 430, 433-CCPA 1977).

Therefore, the reference deems to anticipate claims 1-7, 10, 12, 14-18 and 20.

Claim Rejections - 35 U.S.C. § 103

17. In view of applicants' amendments and arguments filed 18 October 2004 to Office Action mailed 16 April 2004, Examiner hereby withdraws the rejection under 35 USC § 103 (a) to claims 1-10 and 12-24 over Yoshikawa et al. (U.S. Patent 5,369,015) in view of Brunner et al. (U.S. Patent 5,407,803) and further in view of Ryan et al (U.S. Patent 4,355,041).

18. The following new rejection is made including new references, Weinshilboum et al. (American Journal of Human Genetics, 1980,Volume 32, Pages 651-662) and Alegret et al. (European Journal of Pharmacology, 1998, Volume 347, Pages 283-291) because the amended Claims 1 and 12 filed 20 October 2004 add new limitation of "comparing the activity of enzyme in a sample taken from a patient that may or may not have the target drug, against the sample taken from another patient known to have taken the target drug, wherein latter sample is taken as the standard. Both, Weinshilboum et al. and Alegret et al. teach said limitations in a method to determine the enzyme activity in samples obtained from two different patients.

19. Claims 1, 3-10, 12, 14-20 and 22-24 rejected under 35 U.S.C. §103(a) over Weinshilboum et al. (American Journal of Human Genetics, 1980,Volume 32, Pages 651-662) in view of Alegret et al. (European Journal of Pharmacology, 1998, Volume 347, Pages 283-291) and further in view of Brunner et al. (U.S. Patent 5,407,803).

Teachings from each of Weinshilboum et al. and Alegret et al. have been discussed *supra.*

Weinshilboum et al., however, do not teach a method to evaluate ACE activity via measuring the optical density of the reaction mixture. They also do not teach that the drug that inhibits enzyme activity is enalapril.

Brunner et al. teach determining a drug in a human body sample, wherein said drug is an ACE inhibitor. Furthermore, Brunner et al. compare the measured ACE activity in plasma samples taken before and after ingestion of enalapril and compare those activities with a base line and a standard curve for the ACE activity (Column 4, Lines 8 to 53 and Table 1).

One having ordinary skill in the art at the time that said invention was made, would have been motivated to modify/combine Weinshilboum et al's teachings according to the teachings from Alegret et al. and Brunner et al. to obtain instantly claimed method, because Alegret et al. teach a method to measure ACE activity as a function of ACE inhibitor dosage in fluid samples obtained from a patient who may or may not be on an ACE inhibitor and compare said ACE activity with a standard curve constructed on the basis of ACE activity measurements in fluid sample from another patient. Brunner et al. remedy

the deficiency in Weinshilboum et al's teachings because Brenner et al. determine a drug in a patients' plasma, wherein said drug is an ACE inhibitor (i.e., enalapril). Brenner et al also compare the measured ACE activity in plasma samples via comparing said activity with a standard curve.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine Weinshilboum et al's teachings with Alegret et al's and Brunner et al's because all of the cited prior art references teach determining an enzyme activity in presence and absence of a drug, wherein said drug is an inhibitor of said enzyme. Alegret et al. remedy the deficiency in teachings from Weinshilboum et al. of measuring said enzyme activity in absence and presence of said inhibitor (i.e., a statin) and comparing said enzyme activity with a standard curve obtained from measuring said enzyme activity in another patient's fluid and Brunner et al. remedy the deficiency in Weinshilboum et al's teachings of measuring said enzyme activity when ACE inhibitor is enalapril. Instantly claimed assay conditions are not exactly the same as those in prior art. However, the adjustment of particular conventional working conditions (e.g., the quantities of each one of components in reaction mixture, enzyme assay conditions) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter that is well within the purview of the skilled artisan.

From the teachings of the cited references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

CONCLUSION

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR §1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR §1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. For the aforementioned reasons, no Claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 8:15 A.M. to 6:45 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743 Monday through Thursday. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kailash C. Srivastava, Ph.D.
Patent Examiner
Art Unit 1651
(571) 272-0923

January 5, 2005